Evidence Supporting Extracorporeal Shockwave Therapy for Acute and Chronic Soft Tissue Wounds

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Abstract:

Soft tissue wound healing is a complex and well-orchestrated sequence of events on multiple biological levels involving systemic, cellular, and molecular signals. The physiological process of wound healing leads to full tissue repair and regeneration with nearly complete restoration of tissue integrity and functionality.

Wounds, particularly among the elderly population, can show delayed or disturbed healing; however, delayed or disturbed healing is also evident in patients with comorbidities such as diabetes, atherosclerosis, venous/arterial insufficiency, reduced mobility due to chronic infirmity, and hypercholesterolemia.

Chronic wounds consist of a wide range of inflammatory and degenerative conditions of the musculoskeletal system. Management of chronic, difficult to heal, or non-healing soft tissue wounds requires a multidisciplinary approach. Often these treatment options have inconsistent and irregular outcomes. Poor response or failure to conservative treatments places a substantial burden on patients, their families, the healthcare system, and society in general. Therefore, the development of a new, effective method of treatment to improve healing of problematic wounds and reduce treatment-related costs is extremely valuable; ne such therapy is Extracorporeal Shockwave Therapy (ESWT).

ESWT acts through mechanotransduction, which produces therapeutic benefits through complex biological pathways including neovascularization and tissue regeneration in the therapeutic target. Published data thus far suggest that the application of ESWT for soft tissue indications is safe, reliable, cost-effective, and clinically efficacious. The exact biological effects of ESWT on human cells are not completely understood, but are currently undergoing further study.

The aim of this review is to provide a general overview of shockwave therapy and its role in the treatment of acute and chronic soft tissue wounds.

Surgical wounds are the most common wounds in the world. Worldwide, more than 110 million surgical incisions are made every year. In approximately 80% of these cases, some form of closure product is used, such as sutures, staples, and tapes.[1] Many promote hemostasis (blood

clotting), and of course, the use of fabric bandages and surgical dressings is almost universal. Traumatic wounds occur at a rate of about 1.6 million cases each year, and their complexity requires surgical intervention (multiple debridements, skin grafts, skin flaps), especially in military settings. According to the American Burn Association, approximately 450,000 patients with burn injuries seek help in emergency departments annually with more than 40% of these burns involving the upper extremities. Close to 5% of these injuries are full-thickness, third degree injuries.[2]

Occasionally, acute wounds fail to advance through normal physiological steps in a timely manner. The inability of the healing process to progress leaves the wound susceptible to infections and deterioration of the underlying tissue, which typically leads to further morbidities[3-6] and delayed healing. Chronic wounds are defined as wounds that have not proceeded through orderly and timely phases of tissue repair in order to produce anatomic and functional integrity within 3 months.[7]

A number of population-based factors including advanced age, obesity, diabetes mellitus, and venous and arterial insufficiency, have led to an increasing number of patients with chronic wounds. Chronic wounds are placing a great burden on patients, their families, society in general, and the healthcare system in particular. Five to $10 billion is spent annually in the United States for the treatment of chronic wounds,[8] and in Europe, this expenditure accounts for nearly 2% of the healthcare budget.[9] Disturbed wound healing may have different underlying etiologies but generally has a similar appearance. More than 80% of all chronic wounds are attributable to venous/arterial insufficiency, high blood pressure, infection, and diabetes mellitus.[8] Other contributing factors include poor nutritional status, immunosuppression, and tobacco use. Most common chronic wounds involve the lower extremity.[10]

The primary goal of wound treatment and management is durable wound closure and complete healing. In acute wounds, standard of practice includes wound bed preparation, surgical and enzymatic debridement with subsequent application of specialized dressings to provide a moist environment, or surgical closure primarily or with skin grafts or flaps depending on the nature and extent of wounding. To accomplish the same goal of rapid healing in chronic wounds, a multidisciplinary approach is required including diabetes control, nutritional support, wound care with modern dressings (eg, semipermeable films, gels, hydrocolloids, and calcium alginates), use of antibiotics to treat infection, mechanical off-loading, compression therapy for venous stasis and lymphedema, and targeted treatments that promote angiogenesis and vasculogenesis. These therapies are time and labor intensive and costly particularly given the time (weeks to months) it generally takes to achieve wound healing. Therefore, the need for new, safe, efficient and cost-effective treatment is clear and much research has been devoted to development of such a wound therapy. Many adjunctive therapies have been developed and implemented in the care of acute and chronic wounds, including hyperbaric oxygen therapy (HBOT), ultrasound, recombinant human platelet-derived growth factor-BB (rPDGF-BB), negative pressure wound therapy (NPWT); however, safety and efficacy of these and other modalities have yet to be determined.

Wound healing is a well-coordinated, interconnected sequence of biological events on multiple levels—systemic, cellular, and molecular. Wound healing involves a broad variety of cells and events, which are interdependent with overlapping duration and the presence of cell-to-cell signaling molecules within the traumatized tissue. Re-establishment of a functional vasculature is the most critical determinant of restored tissue structure during wound healing,[11] which largely occurs via angiogenesis, specifically endothelial sprouting from the pre-existing local vasculature[12-14] and vasculogenesis, and *de novo* formation of the small blood vessels.[15-16]

The fortuitous initial experimental observations by Valchanov et al[17] who discovered that ESWT activates osteoblasts and is associated with concomitant increase in bone density and calcification led to the first clinical studies of therapeutic shockwave application for bone indications. Around the same time (1980s), evidence emerged regarding the feasibility of ESWT to stimulatate wound healing. However, a rigorous, systematic research approach for investigation of the effects of ESWT on wound healing and underlying mechanism(s) of action began only more recently.

Previous laboratory studies and initial clinical trials have demonstrated that ESWT may be useful and effective through its stimulation of numerous endogenous growth factors in animal models,[18-21] its enhanced recruitment of endothelial progenitor cells,[22] and induction of angiogenesis.[23,24] Nitric oxide (NO), a potent vasodilatation mediator, was greatly increased after the ESWT treatment leading to improved tissue perfusion. One of the mechanisms for long-term improvement of tissue perfusion after ESWT has been shown in an ischemic flap using a rat model.[25,26] Shockwave enhances NO production

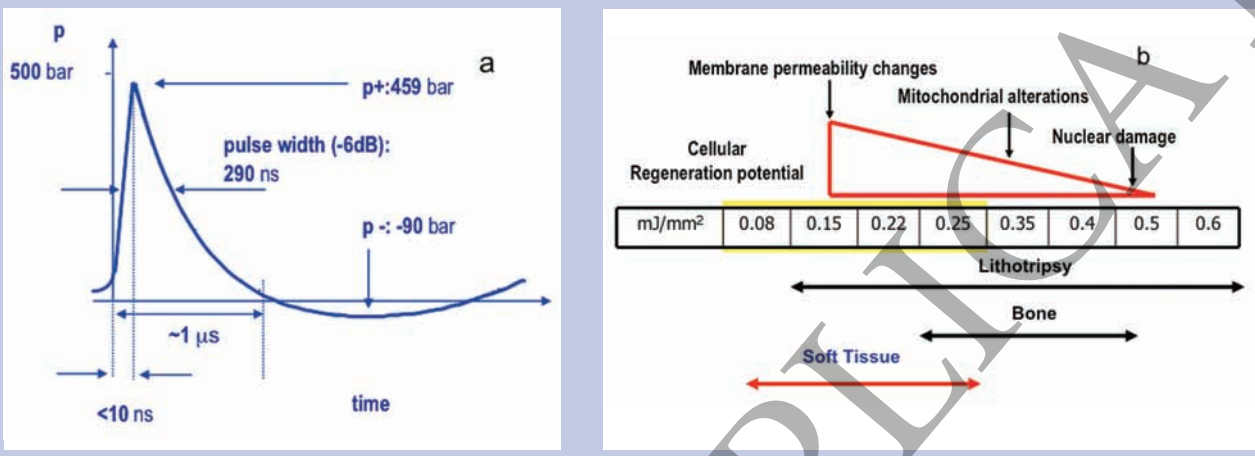

Figure 1. a) Pressure change over time during 1 shockwave. b) Schematic representation of the energy spectrum generated by ESWT and its clinical use.

through increased expression of NO synthase. The most potent endogenous pro-angiogenic and vasculogenic factor, vascular endothelial growth factor (VEGF), is acutely induced[27] after the shoc kwave, and VEGF receptors are more highly expressed in targeted tissue.[28–30]

In animal models, ESWT has been shown to produce favorable molecular microenvironment in the wound tissue, suppress early pro-inflammatory cytokines and c hemokines, and enhance expression of several wound healing relevant genes[19,31]: ELR-positive CXC chemokines, CC chemokines, and cytokines. They were also able to demonstrate enhanced earl y local inflammatory responses (high levels of macrophage-derived inflammatory protein [MIP-1α, MIP-1β]) in the sham treated animals compared to ESWT-treated grafts indicating an anti-inflammatory mechanism of shoc kwaves. Furthermore, shockwaves significantly reduced infiltration of leuk ocytes and macrophages into the isograft. Studies have demonstrated attenuated early local inflammatory responses (low levels of macrophage-derived inflammatory protein [MIP-1a, MIP-1b]) in grafts in ESWT treated animals indicating an anti-inflammatory mechanism of shockwaves.[18,32]

ESWT enhances cell proliferation, stimulates extracellular matrix metabolism, decreases apoptosis[22,33,34] at the local wound tissue level, and down-regulates oxygen-regulated burst of leukocytes and leukocyte infiltration into the isograft.

Table 1. ESWT for soft tissue indications treatment parameters.

Principle	Electro-hydraulic	Electro-magnetic	Piezo-electric	Radial
Energy flux density	0.05–0.20 mJ/mm²	0.15–0.30 mJ/mm²	0.15–0.35 mJ/mm²	2–3 bar
Frequency	3–5	3–5	4–6	10–20
No. pulses	800–2000	1500–3000	1500–2500	1000–3500
No. treatments	1–3	1–3	2–4	3–8
Interval	1–2 weeks	1–2 weeks	1–2 weeks	1–2 weeks

Keypoints

- Occasionally, acute wounds fail to advance through normal physiological steps in a timely manner. The inability of the healing process to progress leaves the wound susceptible to infections and deterioration of the underlying tissue, which typically leads to further morbidities and delayed healing.
- In animal models, ESWT has been shown to produce favorable molecular microenvironment in the wound tissue, suppress early pro-inflammatory cytokines and chemokines, and enhance expression of several wound healing relevant genes: ELR-positive CXC chemokines, CC chemokines, and cytokines.

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy has been in use since the 1980s primarily as a treatment for urinary stones (lithotripsy). Shockwaves are defined as a sonic pulse characterized by a high peak pr essure (500 bar), short

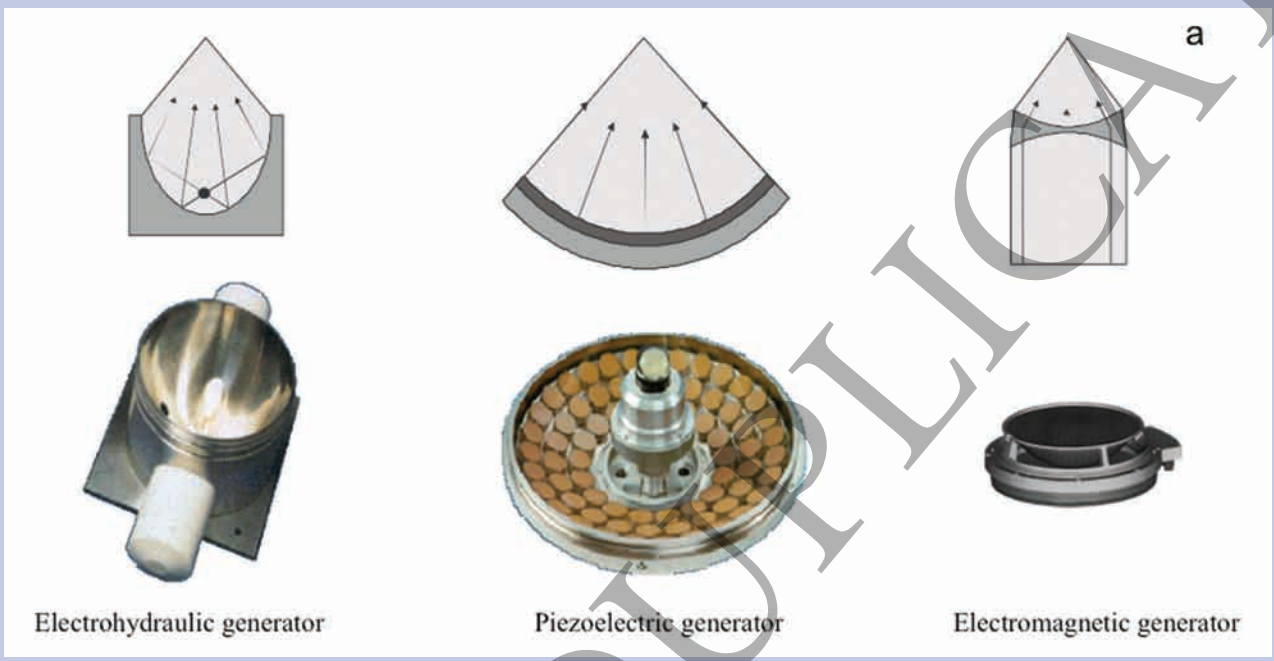

Figure 2a. Shockwave generators and schematic representation of the shockwave front eradiation in electrohydraulic, piezoelectric, and electromagnetic shockwave generators. Electromagnetic and piezoelectric sources only produce a typical shockwave in the focal area (focused extracorporeal shockwave therapy), whereas electrohydraulic systems also produce shockwaves outside the focal area (radial, defocused shockwave therapy) for treatment of larger target areas.

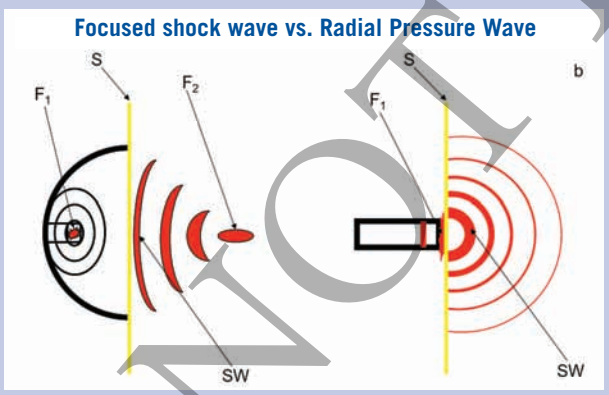

Figure 2b. Focused vs. defocused shock wave therapy. F_1: Focal point in the generator. S: Skin surface. F_2: Focal point (focus and depth of the energy transmitted via shockwaves in the tissue). SW: Shockwaves.

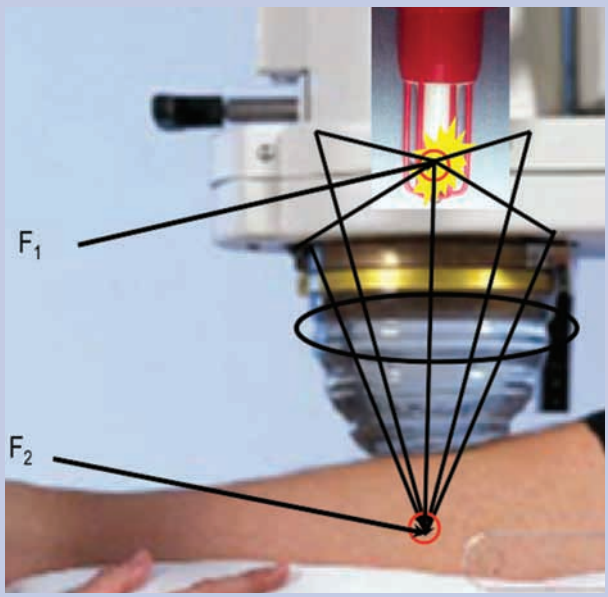

Figure 3. Focused shockwave with focal point (F_1) in the sparkplug of the electrohydraulic generator and focal point (F_2) at defined distance within the tissue. Positioning the opposing electrodes at the primary focus (F_1) in a parabolic reflector results in a planar wave, which is emitted after the reflection of the primary spherical wave. The focal point (F_2) of these plane waves is at an endless distance from F_1.

lifecycle (10 ms), fast pressure rise (< 10 ns), a broad frequency spectrum (16 Hz–20 MHz), and the generation of high stress forces upon interfaces (Figure 1a). The physical energy of shoc kwaves is mec hanotransduced into favorable biological effect on str uctures such as bones and soft tissue with undeter mined mechanisms. Shockwave energy, frequency of the generated waves, number of pulses, and the n umber and inter val of re-treatments are crucial characteristics of treatment description, and are imperative for comparing the different ESWT studies

Table 2. ESWT indications according to the International Society for Medical Shockwave Treatment.

Approved standard indications	Common empirically tested clinical uses	Exceptional/expert indications and experimental
Chronic Tendinopathy Plantar fasciitis* Achilles tendon Tennis elbow Rotator cuff* Patellar tendon Greater trochanter	Chronic Tendinopathy Ulnar epicondylopathy Adductor syndrome Pes anserinus syndrome Peroneal tendon syndrome	Exceptional/Expert Spasticity Early stage OD (pre-skeletal maturity) Osgood-Schlatter's Disease Peyronie's Disease
Impaired bone healing Delayed bone healing Non-unions* Stress fracture Early stage AVN Early stage OD (post-maturity)	Muscular pathology and impaired soft tissue healing Myofascial syndrome Muscle injury w/o discontinuity Impaired wound healing/burns	Experimental Myocardial ischemia Peripheral nerve lesions Abacterial prostatitis Periodontal disease Osteoarthritis
Urologic lithotripsy	Salivary stones	Cellulitis

and standardizing shockwave treatment for various indications. The acoustic pressure wave can be generated by a variety of physical principles that impact these treatment parameters (Table 1). Figure 1b represents the spectrum of energy generated by ESWT according to clinical indication—soft tissue, bone, and kidney stones. As the energy increases the biological effects switch from regeneration to destruction. Energy flux density for soft tissue indications is typically in the range of 0.08–0.25 mJ/mm^2. Focused, high-energy ESWT is utilized for delayed union and non-union of fractures, as well as lithotripsy; however, defocused, low-energy shockwaves are applied for soft tissue indications.

Shockwaves for use in medicine can be generated using different physical principles: electrohydraulic, electromagnetic, piezoelectric, and radial (Figure 2a). It is important to note that electromagnetic and piezoelectric sources only produce a typical shockwave in the focal area, whereas electrohydraulic systems produce shockwaves outside of the focal area as well. Figure 2b shows the differences in the acoustic pressure waves produced between electrohydraulic and radial shockwave sources.

Electrohydraulic. The original method of shockwave generation (used in the Dornier HM3) was electrohydraulic, meaning that the shockwave is produced via spark-gap technology. Electrohydraulic (Spark Gap) systems incorporate an electrode (spark plug) submerged in a water-filled housing comprised of an ellipsoid and a patient interface. The electrohydraulic generator initiates the shockwave by an electrical spark produced between the tips of the electrode (Figure 3). Vaporization of the water molecules between the tips of the electrode produces an explosion, thus creating a spherical shockwave. The shockwave is then reflected from the inside wall of a metal ellipsoid to create a focal point of shockwave energy in the target tissue.

Electromagnetic. Electromagnetic systems utilize an electromagnetic coil and an opposing metal membrane. A high current pulse is released through the coil to generate a strong magnetic field, which induces a high current in the opposing membrane. The magnetic field, in turn, induces a high current in the opposing membrane and accelerates the metal membrane away from the coil. These electromagnetic forces induce a slow and low acoustical pulse that is focused by an acoustic lens to direct the shockwave energy to the target tissue.

Piezoelectric. The piezoelectric effect produces mechanical stress via application of electricity. Piezoelectric ceramics or crystals, set in a water-filled container, are stimulated via high-frequency electrical pulses. The alternating stress/strain changes in the material create ultrasonic vibrations resulting in the production of a shockwave.

Radial. While focused ESWT is used to produce effects in deeper tissue and deliver higher density flux of energy to the tissue and can be used rather for destruction (0.15–0.6 mJ/mm^2), ie, urinary stone lithotripsy, shockwaves indicated for soft tissue application are utilized for treatment of larger areas and delivery of lower energy density flux (0.08–0.25 mJ/mm^2). In wound care, typically a larger surface area is necessary to achieve energy transfer via the

Table 3. Recently published literature of common, empirically tested clinical uses of ESWT for soft tissue indications.

Author	Year	Study Type	Indication	n	ESWT type	EFD (mJ/mm^2)	Outcome	ESWT	Control	Result
Dumfarth	2008	Prospective, randomized trial	Prophylactic low-energy ESWT after vein harvesting	100	EH	0.1	ASEPSIS score; wound infection	4.4 ± 5.3; 4%	11.1 ± 8.3 22%	POS
Saggini	2008	Comparative, case-control study	Chronic wounds	40	EH	0.037	Wound exudate, granulation, size	↓exudate, ↑granulation, ↓wound size	--	POS
Larkin	2010	Prospective, randomized cross-over trial	Chronic wounds; decubitus ulcer	9	EH	0.1	Complete healing	All static chronic ulcers showed improved healing	All static chronic ulcers showed improved healing	POS
Moretti	2009	Prospective, randomized trial	Chronic wounds; diabetic foot ulcer	30	EH	0.03	Complete healing	55% 60.8 ± 4.7 days	33% 2.2 ± 4.7 days	POS
Wang	2011	Prospective, randomized trial ESWT vs. HBOT	Chronic wounds; diabetic foot ulcer	76	EH	--	Complete healing; improved healing; no change in wound	57%; 32%; 11%	25%; 15%; 60%	POS
Wang	2009	Prospective, randomized trial ESWT vs. HBOT	Chronic wounds; diabetic foot ulcer	34	EH	0.11	Complete healing; no change in wound	31%; 11%	22%; 28%	POS
Sanuwave, Inc.	2010	Prospective, randomized trial	Chronic wounds; diabetic foot ulcer	206	PACE	--	Reduction in wound size at 12 weeks; wound closure ≥ 90%	56%; 45%	7%; 26%	POS
Schaden	2007	Prospective feasibility trial	Complex acute and chronic wounds	208	EH	0.1	Complete healing	75%	--	POS

Table 3. Recently published literature of common, empirically tested clinical uses of ESWT for soft tissue indications.

Author	Year	Study Type	Indication	n	ESWT type	EFD (mJ/mm^2)	Outcome	ESWT	Control	Result
Arno	2010	Prospective feasibility trial	Acute wounds, < 5% TBSA full- or partial-thickness burns	15	EH	0.15	Complete healing, tissue perfusion	80% healed, ↑perfusion	--	POS
Ottomann	2010	Prospective, randomized trial	Acute wounds, skin graft donor sites	28	EH	0.1	Time to complete epithelialization	13.9 ± 2.0 days	16.7 ± 2.0 days	POS
Ottomann	2011	Prospective, randomized trial	Acute wounds, superficial second degree burns	50	EH	0.1	Time to complete epithelialization	9.6 ± 1.7 days	12.5 ± 2.2 days	POS

shockwave therapy, and the head has a parabolic instead of an ellipsoid reflector. Positioning the opposing electrodes at the primary focus (F_1) in a parabolic reflector will result in a planar wave, which is emitted after the reflection of the primary spherical wave. The focal point (F_2) of these plane waves is, by definition, "unfocused" or "radial." The parabolic reflector allows the plane waves to be nearly parallel. The energy density realized by this reflector configuration is higher than with an exact parabolic reflector, and the acoustical field stimulates a larger area.

Over the last 15 years, ESWT has emerged as a noninvasive, safe, clinically efficacious, and cost-effective treatment option. ESWT has been approved, is commonly used, or has been in various phases of experimental testing for more than 25 indications (Table 2).

Keypoints

- Shock waves for use in medicine can be generated using different physical principles: electrohydraulic, electromagnetic, piezoelectric, and radial.
- Electromagnetic and piezoelectric sources only produce a typical shockwave in the focal area, whereas electrohydraulic systems produce shockwaves outside of the focal area as well.

An overview of recently published literature of common empirically tested clinical uses of ESWT for soft tissue indications is shown in Table 3.

Studies of ESWT for Acute Soft Tissue Indications

The safety and feasibility of defocused, low-energy ESWT for soft tissue indications was reported in 2007.[35] More than 200 patients were prospectively enrolled into a feasibility trial consisting of complicated, non-healing, acute and chronic soft tissue wounds. According to wound size, every 1 to 2 weeks (over mean 3 shockwave treatments) 100 shocks/cm^2 at 0.1 mJ/mm^2 were applied as an adjunct to standard practice consisting of debridement and moist dressings, which patients tolerated well in an outpatient treatment setting. Of 208 patients, 75% reached 100% epithelialization, and during 44 days of follow up showed no treatment-related toxicity, infection, or wound deterioration in any ESWT-treated wound.

In 2008, a group from Vienna[36] evaluated the prophylactic potential of ESWT in patients undergoing coronary artery bypass graft surgery. One hundred patients were randomly assigned to one of two groups: control (received institutional standard of care; n = 50) and ESWT group that received a total of 25 impulses (energy flux

density of 0.1 mJ/mm ^{2}; 5 Hz) per centimeter of saphenous vein graft donor site wound length, after surgical wound closure under sterile conditions. There were no ESWT-associated adverse events. ASEPSIS score (**A**dditional treatment, presence of **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of the deep tissue, **I**solation of bacteria, and duration of inpatient **S**tay) was significantly higher (P = 0.0001) in the control group suggesting significant improvement in the ESWT-treated group (4.4 ± 5.3 versus 11.6 ± 8.3). In this study, a higher incidence of wound healing disorders necessitating antibiotic treatment was observed in the control group (22%) compared to the ESWT group (4%; P = 0.015). This finding is consistent with reported bactericidal/bacteriostatic effect of ESWT[37–40] and supports the utility of ESWT as a preventive treatment option for saphenous vein harvest wound sites in the setting of coronary graft surgery.

In 2010, Ottoman et al [41] suggested that a single application of ESWT immediately after split-thickness skin graft harvest accelerates donor site epithelialization. They evaluated the effects of ESWT on donor site healing in 28 patients with traumatic wounds and burns that required skin grafting. Patients were randomly assigned to receive standard topical therapy (nonadherent silicone mesh [Mepitel®, Mölnlycke Health Care, Norcross, GA] and antiseptic gel [polyhexanide/octenidine]) to graft donor sites with (n = 13) or without (n = 15) defocused, low energy ESWT (100 impulses/cm^2 at 0.1 mJ/mm^2) applied once to the donor site immediately after skin harvest. Independent blinded observers determined the primary endpoint, which was time to complete epithelialization. The ESWT-treated group had a significantly (P = 0.0001) shorter time to complete epithelialization (13.9 ± 2.0 days) compared to controls, which received only standard dressings (16.7 ± 2.0 days).

The effects of ESWT in a severe full-thickness burn injury was also investigated in an animal model, showing ESWT-related attenuation of both CC- and CXC-c hemokine expression, acute pro-inflammatory cytokine expression, and extracellular matrix proteolytic activity at the burn wound margin.[18] In the wound area, excessive inflammatory responses involving increased levels of inflammatory cells, pro-inflammatory cytokines, and proteases may be attenuated with ESWT allowing wound healing to progress by way of normal physiological repair processes.[19]

In 2010, the results of a clinical trial evaluating the effects of ESWT on deep partial- and full-thickness burns in 15 patients with < 5% of total body surface area burns were published. Arno et al [42] evaluated burn area perfusion with Laser Doppler Imaging system and reported that all burns had significantly increased perfusion after ESWT treatment. The authors also reported that in less than 3 weeks 80% healed completely, 15% required surgical debridement, and 5% developed hypertrophic scarring. Their findings suggest that ESWT may decrease the need for surgical intervention and associated morbidities in patients with severely deep partial- or full-thickness burns.

Together with these findings, and given its proven clinical success, ESWT was further studied in a prospective Phase II clinical trial of 50 patients with second degree burns randomly assigned to standard burn wound care with or without ESWT from December 2006 to December 2007.[42] The control group received burn wound debridement/topical antiseptic therapy. The intervention group, in addition to the same standard therapy, also received low energy, defocused ESWT (100 impulses/cm² at 0.1 mJ/mm², ~20 seconds/cm ^{2}) applied as a single treatment within 24 hours of superficial second degree burn wound debridement. The primary endpoint, time to complete burn wound epithelialization, was determined by an independent, blinded observer. Mean time to complete burn wound epithelialization in the ESWT-treated group was significantly (P < 0.0005) shorter than in controls, 9.6 ± 1.7 versus 12.5 ± 2.2 days, respectively.

Studies of ESWT for Chronic Soft Tissue Indications

In 2008, Saggini et al[43] conducted a preliminary study to investigate the feasibility of ESWT in the treatment of lower extremity chronic ulcers. They enrolled 40 consecutive patients (30 assigned to receive ESWT in addition to conservative dressings and 10 as control group treated with standard dressings only). A total of 32 wounds were treated with ESWT and 16 healed during the 6 treatment period. The other 50% that did not heal showed significant decrease of wound size, and amount of exudates associated with ESWT. Formation of granulation tissue was also significantly more abundant in the shockwave-treated group compared with controls. Relative to controls, ESWT was associated with significantly (P = 0.001) decreased pain, which is consistent with the findings of others.[44,45]

Among the most serious complications of diabetes is a chronic ulcer that can lead to limb amputation. Following the finding that ESWT increases local tissue perfusion and improves angiogenesis, Moretti et al[46] conducted a prospective, randomized, controlled study with 30 patients

affected by neurotrophic diabetic foot ulcers. Patients were randomly assigned to receive either standard of care (debridement, off-loading, and treatment of infection) or standard of care plus ESWT. Healing was evaluated by measuring the rate of epithelialization during a 20-week study period. Complete wound healing was observed in 53% of shockwave-treated patients compared to 33% in patients treated with standard of care alone. Time to complete healing was also significantly improved in the ESWT group (61 vs. 82 days; $P = 0.001$).

In a double-blinded, randomized, crossover study, Larkin et al[47] measured the healing rate of static, chronic ulcers in 8 patients with chronic neurological conditions and chronic decubitus ulceration after ESWT treatment. Of 9 ulcers included in the study, 5 were on the buttocks, sacrum, and trochanter, and 4 were on the distal extremity. Patients were randomly assigned to receive ESWT or placebo treatment for 4 weeks. After this 4-week period and a 2-week washout period, study crossover to the other treatment ensued. Interestingly, regardless of which group they belonged to (initial treatment group or cross-over treatment group) all 9 ulcers showed significant improvement (average of 3 measurements of ulceration were recorded) at 6–8 weeks after the initial shockwave treatment.

Therapeutic wound oxygenation improves wound healing and prevents infection as shown in animal models and in clinical trials.[9] It is commonly used as an adjunct to the treatment of chronic, diabetic foot ulcers applied either topically or through hyperbaric chambers.[48–51] Hyperbaric oxygen therapy (HBOT) is applied for 60–120 min, 5 times per week for a total of 10–30 treatments. Wang et al[52] reported that ESWT appeared to be more effective than HBOT. Seventy-two patients with 72 chronic diabetic foot ulcers were enrolled and randomly divided into two groups: 34 patients with 36 ulcers in the ESWT group and 36 patients with 36 ulcers in the HBOT group. The ESWT group received 300 + 100/cm^2 impulses of shockwave at 0.11 mJ/cm^2 energy flux density every 2 weeks for a total of 6 weeks, whereas patients in the HBOT group received HBOT daily for 20 treatments. Outcome variables included clinical assessment of the ulcers with photo documentation, blood flow perfusion scan, bacteriological examination, histological study, and immunohistochemical analysis. In the ESWT group, 31% completely healed, 58% of wounds improved, and 11% remained unchanged versus 22% completely healed, 50% improved, and 28% unchanged in the HBOT group. Improved local perfusion and increased cell concentration and activity were shown in the ESWT group. On a tissue level, the ESWT group demonstrated significant increases in endothelial nitric oxide synthase, vessel endothelial growth factors, proliferation of cell nuclear antigen expression, and a decrease in transference-mediated digoxigenin-deoxy-UTP nick end-labeling expression. The same authors repeated the evaluation in 2011.[53] The ESWT group consisted of 39 patients with total of 44 chronic diabetic foot ulcers while the HBOT group consisted of 38 patients and 40 foot ulcers. The ESWT group received shockwave therapy twice per week for a total of six treatments, and the HBOT group received hyperbaric oxygen therapy daily for a total 20 treatments. Clinical results showed completely healed ulcers in 57% and 25% ($P = 0.003$); ≥ 50% improved ulcers in 32% and 15% ($P = 0.071$); unchanged ulcers in 11% and 60% ($P < 0.001$) and none worsened for the ESWT and the HBOT group, respectively. Another interesting observation was that even though prior to study-based treatment levels of oxygenation were comparable, oxygenation levels were significantly higher after shockwave therapy than after HBOT ($P = 0.002$). On a tissue level, previous results showing increases in cell proliferation and decreases in cell apoptosis in the ESWT group as compared to the HBOT group were confirmed. The authors concluded that in chronic diabetic foot ulcers ESWT demonstrated better results than HBOT through significant improvement in blood flow perfusion rate and cell activity leading to better healing of the ulcers relative to HBOT.

Sanuwave, Inc. recently announced results of their pivotal Phase III clinical trial comparing the dermaPACE™ device (Sanuwave, Inc., Alpharetta, GA) to sham control for treatment of diabetic foot ulcers.[54] Both groups received the standard of care according to the current literature combined with active (dermaPACE group) or inactive treatment (sham group). A total of 206 patients were enrolled in a double blinded, parallel-group sham control, 26-week clinical trial and were randomly assigned to one of the two study groups. Although the treatment group failed to meet its primary outcome, treatment with dermaPACE increased the proportion of diabetic foot ulcers that closed within 12 weeks by 36%, which was not a statistically significant result. Statistical significance was achieved at 12 weeks when 45% of device-treated and 26% of sham-treated patients had ≥ 90% wound closure. At the 12-week time point, 66% of device-treated and 47% of sham-treated patients had ≥ 70% wound closure. Throughout the entire 12-week period patients in the device treated group had reduced wound size compared to sham-treated patients ($P = 0.0038$ at week 6, $P = 0.0018$

KEYPOINTS

- Current literature supports ESWT treatment modality due to its efficacy, reproducibility, and virtually no adverse events.
- Negative effects of chronic inflammation are suppressed after the treatment leading to improved wound healing, improved tissue perfusion, and increased blood vessel formation.
- Difficult to heal and chronic wounds show significant improvement after the treatment with a low rate of wound recurrence.

at week 8, $P = 0.0007$ at week 10, and $P = 0.0041$ at week 12). At the 12-week time point, the average percent reduction in the target ulcer in patients treated with dermaPACE was 56% compared to only 7% in the patients randomized to receive sham treatment. During the 6-month follow up period, only 4.5% of the patients whose wounds closed at the 12-week time point returned due to recurrence.

Conclusion

ESWT for the treatment of urinary stones and orthopedic indications has been tested and shown to be effective. These shockwaves use high energy to destroy the urinary stones or tissue. The primary goal in the treatment of soft tissue wounds is to produce beneficial stimuli in the tissue, which stimulate and support tissue repair and regeneration. In contrast to the focused ESWT, shockwaves for the treatment of acute and chronic wounds are unfocused with low energy flux densities. Mechanism of transduction of mechanical force (shockwaves) into the complex biological response remains unknown, but potential targets are indentified and further research of this promising technology is imperative.

Current literature supports this treatment modality due to its efficacy, reproducibility, and virtually no adverse effects. Negative effects of chronic inflammation are suppressed after the treatment leading to improved wound healing, improved tissue perfusion, and increased blood vessel formation. Difficult to heal and chronic wounds show significant improvement after the treatment with a low rate of wound recurrence. Treatment is clinically effective, non-invasive (no morbidities related to surgery), is well tolerated by patients, does not require anesthesia, and is cost-effective and easy to apply on an outpatient basis.

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